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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,934	02/10/2004	Bo Hansen	366929-018US (396515)	2105

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,934	HANSEN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008 and 28 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *170-224* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *170,173,175-205 and 221-224* is/are rejected.

7)☐ Claim(s) *172,174 and 206-220* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/10/04, 10/12/07* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 05/28/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 01/18/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 05/28/2008, claims 170-224 are pending and currently under examination. Applicant has canceled claims 1-169.

New Claim Objections and Rejections

Claim Objections

Claims 206-220 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 172 and 174 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 172 and 174 are indefinite because they depend from canceled claims and it is unclear what further limitations the claims may encompass. As such, the claims cannot be examined without assumption and have not been further treated on the merits.

New Claim Rejections - 35 USC § 103

The following new ground of rejection is necessitated by claim amendments filed 09/29/2008.

Claims 170, 171, 173, 175-190, 192-205 and 221-224 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al. (U.S. 6,310,044), Bennett et al. (U.S. Patent No. 6,077,709), Koch et al. (US 2003/0032794) and Kurreck et al. (Nucleic Acids Research, 2002, Vo. 30, No. 9: 1911-1918).

The claims are drawn to a compound consisting of 12-50 nucleotides and/or nucleotide analogues wherein said compound comprise a subsequence of at least 8 nucleotides or nucleotide analogues, said sequence of said region is identically present in the sequence having SEQ ID No. 130 and wherein said subsequence comprises at least one nucleotide analogue, wherein the analogues is selected from a group as listed n claim 154, wherein the compound comprises a sequence having beta-D-oxy-LNA and phosphorothioate linkages ad claimed in the configuration as claimed in claims 48-52 and 159-169.

For purposes of prior art, the limitations of claim 170 recited as "wherein said compound comprises a region of at least 8 contiguous monomers" and "wherein the sequence of said region is identically present in the sequence ....(SEQ ID No. 130)" only requires the oligonucleotide to have minimum of 8 contiguous monomers that are identically present in SEQ ID No. 130.

Draper et al. teach an oligonucleotide compound 21 nucleotides in length comprising 13 contiguous nucleotides identically present in SEQ ID No. 130 (see SEQ ID No. 4 of Draper et al.). Draper et al. teach the oligonucleotide compound comprises from 6 to 50 nucleotide analogues (see column 11) and teach the oligonucleotide comprises phosphate and phosphorothioate internucleotide linkages (see columns 10-11 and Table 10, column 26). Draper et al. further teach compositions comprising pharmaceutically acceptable carriers (see column 12, lines 9-18). Draper et al. does not teach compounds comprising analogues such as 5' methyl cytosine, conjugates and pharmaceutical compositions comprising chemotherapeutic agents.

Draper et al. further does not teach antisense compounds comprising locked nucleic acids (LNA) wherein the LNA are thio-LNA, amino-LNA, oxy-LNA or beta-D-oxy-LNA and further do not teach the antisense compound comprises a stretch of 2-6 LNA followed by a stretch of 4-12 nucleotides which is followed by a stretch of 4 LNA.

Bennett et al. teach antisense compound can comprise analogues such as 5 methyl cytosine, phosphate, phosphodiester and phosphorothioate internucleoside linkages (see at least columns 7-8). Bennett et al. further teach compositions comprising pharmaceutically acceptable carriers or diluents (see column 10) and teach

the composition can be attached to a conjugate such as fatty acids and penetration enhancers (see column 12) and further teach the composition further comprises chemotherapeutic agents such as methotrexate and teach the compounds can be used in the treatment of diseases (see columns 15-16). A specific embodiment exemplifying an antisense compound comprising at least 8 nucleotide analogues such as a chimeric antisense compound is shown in Example 16.

Kurreck et al. teach antisense oligonucleotides comprising LNAs improves the affinity for complementary sequences and increase the stability of such oligonucleotides (see page 1912). Kurreck et al. teach incorporation of LNAs into oligonucleotides wherein the LNA are configured as gapmers, a stretch of 2-5 LNA, followed by a stretch of 8-14 nucleotides followed by a stretch of 2-5 LNA increase the oligonucleotide target affinity (see Table 1).

Koch et al. teach antisense compounds comprising LNA are promising new drug candidates and teach preparation of LNA such as amino-LNA and oxy-beta-D-LNA (see paragraph 0013-0014).

It would have been obvious to one of skill in the art to make compounds comprising nucleotide analogues, such as 2'-methoxyethyl and compounds comprising conjugates and chemotherapeutic agents as taught by Bennett et al. It would have been further obvious to incorporate LNA, particularly LNA in a gapmer configuration as taught by Kurreck et al. and Koch et al. into the antisense oligonucleotide taught by Draper et al.

One of skill in the art would have been motivated and it would have been routine to one of skill in the art to incorporate nucleotide analogues such as taught by Bennett et al. and conjugates and chemotherapeutic agents into the compounds and compositions taught by Draper et al. for the purposes of increased stability of the compound and enhanced therapeutics when delivered to cells. One of skill in the art would have been motivated to incorporate LNA into the antisense oligonucleotide taught by Draper et al. because Kurreck et al. teach LNAs improves the affinity for complementary sequences and increase the stability of such oligonucleotides. Further, one would have wanted to improve the target affinity of the antisense oligonucleotide taught by Draper et al. given Draper et al. teach the antisense oligonucleotide can modulate the expression of survivin gene expression which leads to a treatment of such diseases associated with overexpression from said gene, such as cancer. One would have been motivated to incorporate LNA in different configurations and a matter of routine optimization to design antisense oligonucleotide comprising LNA followed by stretch of nucleotides as taught by Kurreck et al. to determine the most efficient configuration of antisense oligonucleotides comprising LNA that allow for maximum stability and target affinity. Moreover, one of skill in the art would have been motivated to specifically incorporate LNA, such as oxy-beta-D-LNA given Koch et al. teach this is a preferred LNA and teach synthesis of oligonucleotide comprises said LNA.

One would have been expected to be able to incorporate nucleotide analogues and conjugates and chemotherapeutic agents as taught by Bennett et al. and further to incorporate LNA into antisense compounds that allow for increased stability and target

affinity given Bennett et al. and Kurreck et al. teach such compounds are capable of inhibition of gene expression and one of skill in the art would have expected to be able to synthesize LNA given Koch et al. details preparation of LNA and incorporation into oligonucleotides.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 170 and 175-201 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altieri et al. (U.S. 6,509,162) and Keys et al. (US Patent No. 6,593,091).

The claims are drawn to a compound consisting of 12-50 nucleotides and/or nucleotide analogues wherein said compound comprise a subsequence of at least 8 nucleotides or nucleotide analogues, said sequence of said region is identically present in the sequence having SEQ ID No. 130 and wherein said subsequence comprises at least one nucleotide analogue, wherein the analogues are configured as instantly claimed.

Altieri et al. teach an oligonucleotide sequence comprising 24 nucleotides wherein 15 contiguous nucleotides are identically present in the claimed SEQ IS NO. 130 (see below).

RESULT 7
AR275640

```
LOCUS       AR275640                 24 bp    DNA     linear   PAT 10-APR-
2003
DEFINITION  Sequence 5 from patent US 6509162.
ACCESSION   AR275640
VERSION     AR275640.1  GI:29709079
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 24)
  AUTHORS   Altieri,D.C.
  TITLE     Methods for selectively modulating survivin apoptosis pathways
  JOURNAL   Patent: US 6509162-A 5 21-JAN-2003;
            Yale University; New Haven, CT
FEATURES             Location/Qualifiers
     source          1. .24
                     /organism="unknown"
                     /mol_type="genomic DNA"
ORIGIN

  Query Match             93.8%;  Score 15;  DB 2;  Length 24;
  Best Local Similarity   100.0%;  Pred. No. 26;
  Matches   15;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          2 TCAATCCATGGCAGC 16
              |||||||||||||||
Db          7 TCAATCCATGGCAGC 21
```

Altieri et al. teach the oligonucleotide can be used as a probe to detect a survivin gene of interest (see SEQ ID No. 5). Altieri et al. do not teach said oligonucleotide comprises modified nucleotide analogues.

Keys et al. teach modification of oligonucleotide sequences useful as probes and primers for detecting the presence of a target sequence or amplifying a target sequence and teach the oligonucleotide can be from 8 to 60 nucleotides in length, can be comprised entirely of nucleotide analogues such as PNA and wherein the monomers are liked by phosphodiester or phosphorothioate linkages (see columns 5 and 6).

It would have been obvious to incorporate nucleotide analogues such as taught by Keys et al. into the oligonucleotide taught by Altieri et al. to increase the binding affinity of the sequence to the target polynucleotide sequence and one of ordinary skill in the art at the time the invention was made would have wanted to increase the binding affinity of said oligonucleotide. One of ordinary skill in the art would have expected to be able to incorporate said analogues as taught by Keys et al. and this would have been a matter of routine experimentation.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Applicant's arguments filed 05/28/2008 have been fully considered but they are not persuasive. Applicant argues Draper does not teach antisense oligonucleotides that modulate survivin gene expression. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., modulation of survivin expression) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, because the instant claims do not recite any functional language associated with the claimed oligonucleotide, the oligonucleotide taught by Draper et al. do not have to teach said

functional language. Furthermore, because the oligonucleotide taught by Draper et al. is identical in structure to the claimed oligonucleotide, a prima facie case of obviousness has been established and the Applicant has the burden of showing the prior art oligonucleotide does not necessarily possess the characteristics of the claimed product.

Applicant further argues that Draper does not disclose any specific modifications to the sugar or base moieties of the oligonucleotide. As pointed out above, Draper et al. does not teach antisense compounds comprising 5'methyl cytosine or locked nucleic acids (LNA) wherein the LNA are thio-LNA, amino-LNA, oxy-LNA or beta-D-oxy-LNA however as shown by Bennett et al, Kurreck et al. and Koch et al, it would have been obvious to one of ordinary skill in the art to incorporate said moieties into the oligonucleotide taught by Draper et al.

Applicant argues that while Kurreck et al. and Koch et al. do in fact teach the use of LNAs in antisense oligonucleotides, they do not suggest these antisense oligonucleotides comprise a region that is identically found in SEQ ID No. 130. In response, one cannot show non-obviousness by attacking the references individually when the rejection is based on the combination of all the references cited. If Kurreck et al. and Koch et al. taught all the claimed limitations they would have been applied as a 102 reference. As stated in the previous Office action, it would have been obvious to one of ordinary skill in the art to incorporate said LNA monomers taught by Kurreck et al. and Koch et al. into the oligonucleotide taught by Draper et al. for the reasons of record.

Applicants argue that as evidenced by Bennett et al., the modulation of gene expression by modified antisense oligonucleotides is unpredictable and it would not have been obvious to modify the oligonucleotide taught by Draper et al. by introducing modified nucleotides as claimed in order to achieve a predictable result of modulating the expression of a gene other than a herpes virus gene.

In response, as stated above the claims do not recite any claimed functional language or any specific requirements for percent inhibition of a target gene. Nonetheless, it was well known in the art regarding the use of antisense oligonucleotides to inhibit the expression of target genes for the purpose of elucidating the role said genes have in the progression of diseases and it was well known in the art that incorporation of sugar and base modifications such as LNAs improves the affinity for complementary sequences and increase the stability of such oligonucleotides. Thus one would have wanted to modify antisense oligonucleotides and would have expected to be able to modify said oligonucleotides as shown by Bennett et al, Kurreck et al. and Koch et al.

Re: Non-statutory Double Patenting

Acknowledgement is made of Applicant's request that the rejection be held in abeyance until allowable matter is indicted in the instant claims, therefore the rejection of claims 3, 5-16, 19-21, 23-38, 45-46, 48-52, 120-124 and 153-169 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of co-pending application 11/272,124 is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

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/Kimberly Chong/
Examiner
Art Unit 1635